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Modeling auditory evoked brainstem responses to transient stimuli

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Abstract

A quantitative model is presented that describes the formation of auditory brainstem responses (ABR) to tone pulses, clicks and rising chirps as a function of stimulation level. The model computes the convolution of the instantaneous discharge rates using the “humanized” nonlinear auditory-nerve (AN) model of Zilany and Bruce (2007) and an empirically derived unitary response function which is assumed to reflect contributions from different cell populations within the auditory brainstem, recorded at a given pair of electrodes on the scalp. It is shown that the model accounts for the decrease of tone-pulse evoked wave-V latency with frequency but underestimates the level dependency of the tone-pulse as well as click-evoked latency values. Furthermore, the model correctly predicts the nonlinear wave-V amplitude behavior in response to the chirp stimulation both as a function of chirp sweeping rate and level. Overall, the results support the hypothesis that the pattern of ABR generation is strongly affected by the nonlinear and dispersive processes in the cochlea.

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I. INTRODUCTION

When sound is presented to the ear, it is possible to record auditory evoked potentials (AEPs) on the surface of the human scalp. AEPs represent the summed electric potential from many remotely located neurons firing in response to the stimulus applied. They are typically grouped in terms of time of occurrence after stimulus onset and are thus denoted as auditory brainstem responses (ABRs) with latencies between 1 and 7 ms, middle-latency responses (MLRs) with latencies in the range of 15-50 ms, and auditory late responses (ALRs) with latencies in the range of about 75-200 ms.

AEPs have been used to assess the neural encoding of sound both for clinical and research purposes. Various types of stimuli have been considered, such as transients like clicks, chirps and tone-bursts (e.g., Jewett and Williston, 1971; Dau *et al.*, 2000), steady-state signals such as amplitude modulated (AM) tones (e.g. John and Picton, 2000; Galambos *et al.*, 1981; Kuwada *et al.*, 1986; Picton *et al.*, 1987; Rees *et al.*, 1986), but also more complex signals like speech (e.g., Warrier *et al.*, 2004; Agung *et al.*, 2006; Swaminathan *et al.*, 2008; Aiken and Picton, 2008; Akhoun *et al.*, 2008; Lalor and Foxe, 2010; Chandrasekaran and Kraus, 2010). Tone-burst evoked ABRs have been studied to objectively estimate frequency-specific hearing sensitivity, for example in newborn and young children (e.g. Ribeiro and Carvallo, 2008) or to estimate effects of cochlear group delay as a function of frequency and level of stimulation (e.g. Gorga *et al.*, 1988; Harte *et al.*, 2009; Neely *et al.*, 1988; Murray *et al.*, 1998). Broadband rising chirps have recently been developed for ABR recordings to maximize synchronous firing of nerve fibers across frequency, leading to an increase of ABR wave-V amplitude and a higher signal-to-noise ratio compared to traditional click stimulation (e.g. Dau *et al.*, 2000; Elberling and Don, 2008; Fobel and Dau, 2004; Junius and Dau, 2005; Shore and Nuttall, 1985). It is argued (Dau *et al.*, 2000), that these broadband chirp stimuli compensate for the frequency-dependent group delay seen in the basilar membrane (BM) velocity/displacement travelling waves. In a recent study, Elberling *et al.* (2010) presented

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five chirps with different frequency-delay functions and investigated the resulting wave-V amplitude of their responses at stimulation levels of 20, 40 and 60 dB normal hearing level (nHL). Their results demonstrated that the dispersion function, or sweeping rate, of the chirp that evoked the largest wave-V amplitude was a function of stimulation level. With increasing level, the “optimal” chirp that created the largest wave-V response was found to become progressively shorter (Elberling *et al.*, 2010), i.e. to have the fastest sweeping rate.

It is well known that the *frequency* dependency of wave-V latency is related to the tonotopical coding of frequency on the BM in the cochlea. High-frequency stimulation excites basal parts of the BM and thus produces a shorter delay than low-frequency stimulation that mainly excites apical parts of the BM (Gorga *et al.*, 1988; Greenwood, 1990; Harte *et al.*, 2009; Neely *et al.*, 1988; Murray *et al.*, 1998). The *level* dependency of wave-V latency is not so well understood. Cochlear tuning is known to be level dependent, where an increase of the stimulus level results in broader auditory filters and thus a broader excitation pattern on the BM (Glasberg and Moore, 1990; Recio and Rhode, 2000). This means that regions of the BM with characteristic frequencies further away from the stimulus frequency are also excited. Elberling (1976) and Folsom (1984) reasoned that the broadening of excitation with level might result in shorter latencies, as more basal regions of the BM are activated that are associated with shorter implicit delays. Another inherent feature of the filter tuning is the change in the envelope of the BM impulse response at a given location, as level is increased. The timing of the individual peaks of the physiological impulse response are level independent but the amplitude of the earlier peaks are more emphasized as the stimulus level increases (e.g., Kiang (1965), Recio and Rhode (2000)). This change in the envelope, as stimulus level is increased, results in an onset emphasis that could result in a decrease of the wave-V latency. Adaptation in the inner-hair cell (IHC)-AN synapse similarly enhances the onset of a signal while attenuating later parts (Westerman and Smith, 1988) in the stimulus. Thus, adaptation in the IHC-AN synapse might also contribute to the level-dependence of wave-V latency.

The wave V amplitude is both stimulus frequency and stimulus level dependent. The

general shape of the frequency dependence is considered to be mainly controlled by the transfer functions of the outer and middle ear effectively acting as a band-pass filter (Pascal *et al.*, 1998; Puria, 2003), with maximal transduction at 1-2 kHz. The level dependence of the wave-V amplitude results from the summation of the individual neural responses after the non-linear processing through the BM at the individual characteristic frequencies (CFs), where compressive behavior has been found for medium-level stimulation at the CF while linear behavior has been found for low-level stimulation (e.g. Ruggero *et al.*, 1997). The chirp-evoked ABRs obtained in Elberling *et al.* (2010) demonstrated non-monotonic level-dependent behavior, assumed to result from the broadening of neural excitation with increasing level (Harte *et al.*, 2010). At low levels, each frequency component of the chirp might excite a narrow region on the BM and, given the timing associated with each component, might add up in phase (e.g. Dau *et al.*, 2000). At high stimulus levels, each frequency component excites a broader region on the BM, due to upwards spread of excitation (Rhode and Recio, 2000). Thus, a specific location on the BM is excited by a broader range of frequency components. These different components contribute with different timing which results in desynchronization and a reduction of ABR wave-V amplitude (Elberling *et al.*, 2010).

However, while it appears obvious that cochlear processing affects ABR amplitudes and latencies, only very few studies have actually attempted to provide quantitative predictions of ABR data. In the present study, a computational model is presented that simulates evoked responses to tone pulses of various frequencies and levels, upward chirps with different sweep rates and levels as well as click stimuli. The key stages in the model are (i) the nonlinear processing in the cochlea, including key properties such as compressive basilar-membrane filtering, inner hair-cell (IHC) transduction, and IHC-AN synapse adaptation, and (ii) the (linear) transformation between the neural representation at the output of the AN and the recorded potential at the scalp. This approach was inspired by Goldstein and Kiang (1958), who described evoked responses as a linear convolution of an elementary unit waveform of

a given neuron, called the unitary response, with the instantaneous auditory nerve (AN) discharge rate in response to a given stimulus. This approach was applied to simulate cat compound action potentials (CAP) by deBoer (1975).

Based on the work of Goldstein and Kiang (1958), deBoer (1975) and Melcher and Kiang (1996), Dau (2003) proposed a model for the generation of ABRs and frequency following responses (FFR) to tones. In Dau (2003), the unitary response was estimated empirically based on measured ABR data, via deconvolution of average click-evoked responses and the simulated neural activity pattern at the output of an AN model. Dau (2003) demonstrated that the auditory periphery strongly affects the simulated ABR patterns and could account for some of the key features observed in the recordings of chirp- versus click-evoked responses. However, while that study provided a proof of concept, it did not consider a more detailed analysis of the responses as a function of stimulation frequency and level. Furthermore, significant discrepancies between the predicted and measured wave-V latencies were observed but not further evaluated. Here, the original modeling framework of Dau (2003) was extended to include current advances in AN modeling, such as linear BM filters at high stimulus levels, peak splitting (Kiang, 1990) and a shift of best frequency with level. The AN model developed by Zilany and Bruce (2007) was used here which is based on current knowledge derived from both behavioral and objective measures of cochlear processing. The model was originally developed for cat but also adopted by the same authors for humans including corresponding middle-ear filtering and BM filter tuning (Ibrahim and Bruce, 2010).

II. MODEL FOR ABR GENERATION

A. Convolution model of ABR generation

Melcher and Kiang (1996) described the generation of ABR in cats as a summation of individual brainstem cell potentials, v_i , in response to a given stimulus, s ;

$$\text{ABR}(t, \bar{x}_1, \bar{x}_2, s) = \sum_i v_i(t, \bar{x}_1, \bar{x}_2, s) \quad (1)$$

where \bar{x}_1 and \bar{x}_2 are the locations of the electrodes on the scalp. The potential, v_i , in response to a given acoustic stimulus, can be determined by a convolution between the instantaneous firing rate of the i^{th} cell, $r_i(t, s)$, and a unitary response function, $u(t, \bar{x}_1, \bar{x}_2)$. This latter function is defined as the potential produced between the electrode positions on the scalp, \bar{x}_1 and \bar{x}_2 , each time the cell discharges;

$$v_i(t, \bar{x}_1, \bar{x}_2, s) = r_i(t, s) \star u_i(t, \bar{x}_1, \bar{x}_2) \quad (2)$$

where \star denotes the convolution operation. To obtain an ABR with this method, all cells need to be considered individually, which would be computationally prohibitive. To avoid this, Melcher and Kiang (1996) suggested the use of the cell population potential, V . Cells can be grouped by the physio-anatomical type of the cell, p , where P is the number of different cell types:

$$\text{ABR}(t, \bar{x}_1, \bar{x}_2, s) = \sum_{p=1}^P V_p(t, \bar{x}_1, \bar{x}_2, s) \quad (3)$$

It is reasonable to assume that all cells of the population described have the same unitary response (UR), $u(t, x_1, x_2)$, as they have the same morphological and electrical properties (Melcher and Kiang, 1996). The combination of eqn. (2) and (3) yields a general expression for ABR generation:

$$\text{ABR}(t, \bar{x}_1, \bar{x}_2, s) = u(t, \bar{x}_1, \bar{x}_2) \star \sum_{p=1}^P \sum_{i=1}^{N_p} r_{pi}(t, s) \quad (4)$$

where N_p is the total number of cells of type, p . The three main peaks in the click-evoked ABR are waves I, III and V. Dau (2003) made the assumption that the instantaneous firing functions in the medial superior olive (MSO), anterior ventral cochlear nucleus (AVCN) are the same as in the AN, following the suggestion by Melcher and Kiang (1996). Thus,

the instantaneous firing functions for the different cell populations are given by $r_{i,\text{MSO}} = r_{i,\text{AVCN}} = r_{i,\text{AN}} = r_i$, simplifying Eqn. 4 to:

$$\text{ABR} = u(t, \bar{x}_1, \bar{x}_2) \star \sum_{i=1}^N r_i(t, s) \quad (5)$$

The generation of an ABR is thus represented as the sum of the instantaneous firing from all cells, convolved with a UR that is dependent on the electrode location on the scalp but assumed to be independent of cell type, efferent influence and stimulus.

B. Model structure

The structure of the ABR model is shown in Fig. 1. The AN model calculates the instantaneous discharge rate for individual AN fibers, in response to a given acoustic stimulus defined in pascals. Each AN fiber is tuned to a specific characteristic frequency (CF). The CFs chosen were spaced according to the human cochlear map of Greenwood (1990). The number of fibers included was a trade-off between computational time and model accuracy. Throughout this study, 500 fibers ranging from 100 Hz to 16 kHz were used in all simulations. The fibers were chosen so they were spaced equally on the BM according to the human cochlear map (Greenwood, 1990). The output of the AN model, the instantaneous firing rate of all the AN fibers, were summed and convolved with the UR function.

The AN model of Zilany and Bruce (2006) is shown schematically in Fig. 2. The input to the AN model is the instantaneous pressure waveform of the stimulus in units of pascals. The output of the AN model is the spike rate in response to the stimulus pressure. The model includes a number of key functional stages: a middle-ear filter; a feed-forward control path; a primary signal-path filter (C1) representing the basilar membrane (BM) filtering adapted by the control path; a parallel-path filter (C2) for high-level stimuli; an inner-hair cell (IHC) section followed by a synapse model and a stochastic AN spike discharge generator. In Fig. 2, the following abbreviations are used: outer hair cell (OHC), low-pass (LP) filter, static nonlinearity (NL), characteristic frequency (CF) and inverting nonlinearity (INV). C_{OHC}

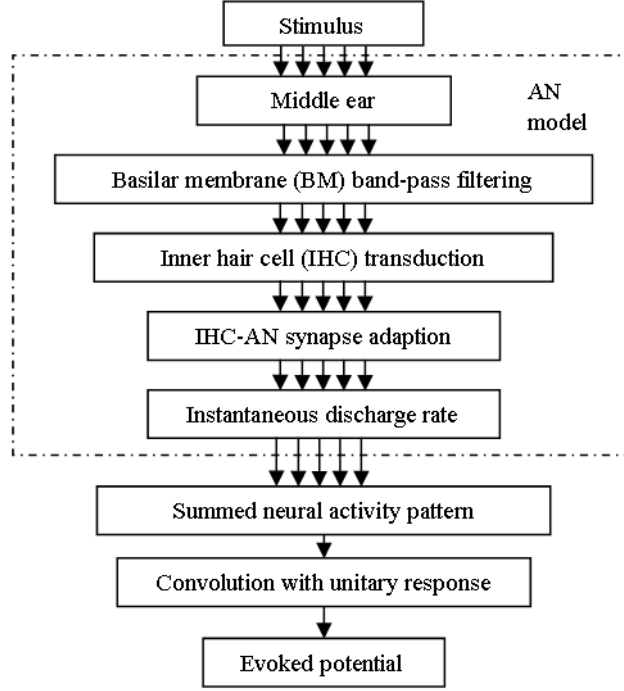


FIG. 1. Schematic structure of the ABR model. 500 AN fibers tuned to different CFs are individually simulated by the AN model. The summed activity, integrated across frequency, is then convolved with a unitary response and represents the simulated ABR to a given stimulus.

and C_{IHC} are scaling constants that indicate the OHC and IHC status, respectively. The black and gray curves in the filter stages represent the tuning at low and high sound pressure levels, respectively. The wideband C2 filter shape is fixed and is the same as the broadest possible C1 filter. The black and gray functions in the stage following the C1 filter indicate the nonlinearity in the IHC input/output functions in normal and impaired (scaled down according to C_{IHC}) hearing, respectively. Details about the model implementation can be found in Zilany and Bruce (2006). In the present study, the spikes/s output from the synapse model was used, rather than the stochastic output from the spike generator. The stochastic spike generator requires averaging over many repetitions before it becomes repeatable and thus usable to ABR modeling.

Bentsen *et al.*, 2011). The sharper human tuning is also probable in light of the recent findings by Joris *et al.* (2011) who showed that macaque monkeys have sharper tuning than rodents and cats. Further, the simulations using the ABR model produced the best results with the Shera *et al.* (2002) tuning compared to the alternative broader tuning presented by Glasberg and Moore (1990). To incorporate the sharper tuning, the model equivalent rectangular bandwidth (ERB) quality factor, Q_{ERB} , for cochlear tuning was modified to be:

$$Q_{\text{ERB}} = 12.7 \left(\frac{CF}{1000} \right)^{0.3} \quad (6)$$

where CF is the center frequency of the BM filter. According to Shera *et al.* (2002), this function is applicable to humans at frequencies at and above 1 kHz. To map the Q_{ERB} to the Q_{10} estimates used by the AN model the following mapping function was used (Ibrahim and Bruce, 2010):

$$Q_{10} = 0.2085 + 0.505Q_{\text{ERB}} \quad (7)$$

Figure 3 shows the quality factor, Q , for the model’s filters for different levels and CFs derived from simulated responses. The Q -values were derived from tuning curves by evaluating the magnitude response at CF to a number of pure tones with equal amplitude covering the frequency range around CF. The output from the C1 filter path was used for this calculation.

Third, cochlear suppression tuning curves have been found to have a peak at a higher frequency than the tip of an excitatory tuning curve (Delgutte, 1990), i.e., maximum suppression has been observed when stimulating at a higher frequency than CF. This was implemented in the original Zilany and Bruce (2006) model by basally shifting the CF of the so-called control path filter by 1.2 mm on the BM. The 1.2 mm basal shift was retained in the humanized model, but Greenwood (1990)’s human frequency-place mapping was implemented to link the 1.2 mm shift to the corresponding characteristic frequency.

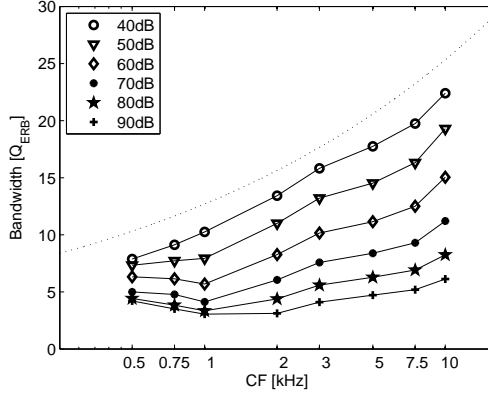


FIG. 3. Filter bandwidths, Q_{ERB} , derived from the output of the C1 filter path (from Fig. 2). The dashed curve shows Q_{ERB} estimates based on Shera *et al.* (2002)’s data obtained at a stimulation level of 40 dB pe SPL.

III. METHOD

A. Estimation of the unitary response

The unitary response (UR) was obtained by deconvolving a “template” click-evoked ABR with the summed neural activity pattern generated by the AN model in response to a click stimulus. Given the assumed superposition, any stimulus should in theory be usable. In this study, a click stimulus was chosen as it is most commonly used in clinics. The deconvolution is an ill-posed mathematical problem and has an infinite number of solutions. A stable and probable solution was, like in Dau (2003), found using Tikhonov regularization (Tikhonov, 1963) as implemented in the MATLAB Regularization Tools of Hansen (1998). The UR is subject dependent. In an attempt to employ a general UR, Elberling *et al.* (2010)’s grand average ABR data (left panel of Fig. 4) was used for the deconvolution. The resulting general UR was advantageous as the simulations presented in this study were compared to reference data, typically averaged across many subjects.

The grand average ABR (Elberling *et al.*, 2010) was made by aligning wave-V peaks across recordings from 20 ears. The stimulus was a 100 μs standard click presented at

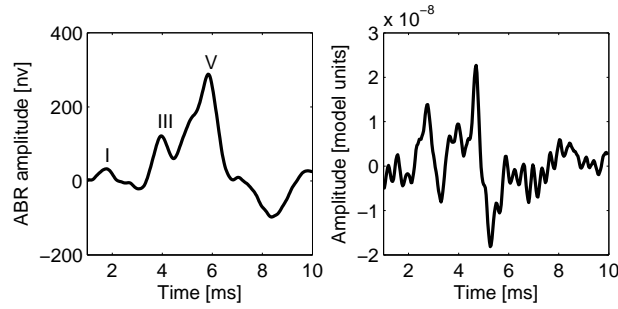


FIG. 4. Left panel: Grand average ABR evoked by 60 dBnHL click (Elberling *et al.*, 2010). Right panel: The derived unitary response function used throughout this study. This was calculated as the deconvolution of the grand average ABR and the summed neural activity pattern generated by the AN model in response to an identical click stimulus.

60 dBnHL (≈ 95.2 dB pe SPL, see section III.B.3 for conversion factor). The alignment procedure created a standardized click-evoked ABR that had the disadvantage that the wave-V amplitude was smaller than in an individually measured ABR, due to inter-subject variability of the individual wave-forms. The UR was therefore scaled such that the simulated click-evoked ABR at 40 dBnHL had the same amplitude as the mean ABR amplitudes (rather than the amplitude of the grand averaged waveforms) from Elberling *et al.* (2010). The right panel of Figure 4 shows the UR, obtained with the grand averaged ABR (from the left panel) as the target. The UR function is similar to the one obtained in Dau (2003). The ABR model using this UR is also capable of simulating the latency of wave-I. Given the linearity of the UR function the wave-I to wave-V interval will remain constant. Simulated wave-I amplitudes will however be smaller due to the way the UR was derived from the grand average ABR. If the model were to simulate wave-I amplitudes, the UR should either be scaled according to a representative wave-I amplitude, or be recalculated based on a click-response where the wave-I is more faithfully represented. In the present model, linear superposition was assumed above the level of the AN synapse; thus, the derived UR function was applied to any input stimulus at any level.

B. Stimuli

1. *Tone bursts*

Hanning-windowed tone bursts as in Harte *et al.* (2009) were used as stimuli. The tone bursts with center frequencies of 2 kHz and above included approximately 10 cycles and therefore ranged from 5 to 1.25 ms (see Table I). The number of cycles during the rise time period was reduced to 7.5 at 1.5 kHz and 5 at 1.0 kHz. These durations represent a trade-off between having an equal number of cycles across frequencies and a relatively narrow spread in their spectrum. Levels of 40 to 100 dB peSPL were used, in steps of 10 dB.

2. *Broadband chirps and clicks*

Five chirps with different delay functions were used as defined in Elberling *et al.* (2010). The frequency-dependent delays of the chirps were defined as:

$$\tau = k \cdot \text{CF}^{-d} \quad (8)$$

where τ represents the latency associated with frequency CF, and k and d are paired constants. Table II lists the parameters representing the individual chirps, following the choices of Elberling *et al.* (2010). The delay difference between 710 and 5700 Hz for the chirps 1 to 5 were thus 1.86, 2.56, 3.32, 4.12 and 5.04 ms, respectively. For comparison, a “standard” click stimulus of 100 μs duration was presented at 20, 40 and 60 dB nHL. The five chirps were calibrated such that they had the same spectrum level as the click.

3. *Calibration of the stimuli*

As the experimental data were described in dB pe SPL or dB nHL, it was necessary to acoustically calibrate the transient stimuli used in this study with an IEC 60711 coupler. The tone bursts and the click were measured acoustically with an Etymotic ER2 earphone connected to an IEC 60711 coupler (Brüel and Kjær 4157) through a Brüel and Kjær external

ear simulator DB 2012. For each stimulus in the tone burst simulation (6 tone bursts and 1 click), the amplitude was adjusted until the acoustically measured peak-to-trough amplitude was similar to the peak-to-trough amplitude of a reference 1-kHz pure tone signal. A scaling factor was found to calibrate the numerical model.

As in Elberling *et al.* (2010), the chirps were adjusted to have the same spectrum level (rather than dB pe SPL) as the calibrated click. Elberling *et al.* (2010) provided the click and chirp levels in dB nHL, and the stimuli needed to be converted to dB peSPL at the eardrum before being presented to the model. The correct conversion factor was found to be 35.2 dB¹ (Richter and Fedtke, 2005), and hence the levels corresponding to 20, 40 and 60 dB nHL were found to be 55.2, 75.2 and 95.2 dB peSPL, respectively.

IV. RESULTS

A. Simulation of tone-burst evoked wave-V latencies

Figure 5 shows the simulated tone-burst evoked ABR wave-V latencies obtained with the ABR model (symbols connected with solid lines). For direct comparison, functions fitted to measured data from Neely *et al.* (1988) are indicated as dashed lines. Neely *et al.* (1988)'s fitted lines were described by:

$$\tau_b = a + bc^{-(i/100)}(CF/1000)^{-g} \quad (9)$$

where i is the tone-burst intensity in SPL (divided by 100), CF is the tone burst center frequency in Hertz, and $a = 5$ ms, $b = 12.9$ ms, $c = 5.0$ and $g = 0.413$ were fitted constants. Additionally, measured data obtained in Harte *et al.* (2009) at a level of 66 dB peSPL are shown as a dotted line. The differences between Neely *et al.* (1988) and Harte *et al.* (2009)'s stimuli resulted in negligible differences in simulation results, therefore only Harte *et al.* (2009)'s stimuli are simulated here. The inter-subject variability (the standard deviation) on the Harte *et al.* (2009) data is 1.36 ms for 1 kHz, 0.93 ms for 2 kHz, and 0.71 ms for 8 kHz. Neely *et al.* (1988) does not explicitly state any inter-subject variability. The click

data (Elberling *et al.*, 2010) showed an inter-subject variability of 0.61 ms, 0.92 ms and 0.91 ms for hence 20 dB HL, 40 dB HL and 60 dB HL stimulus level.

The simulated and measured ABR wave-V latencies decrease exponentially as a function of frequency. At the highest stimulation levels, the simulated latencies are close to those observed in Neely *et al.* (1988). With decreasing level, the rate of change of latency with frequency increases both in the simulations and the measured data. However, the dynamic range of latencies across levels is smaller in the predictions than in the data. This effect is dominant towards higher tone-burst frequencies where latencies of about 6-7 ms were predicted in contrast to 6-8 ms in the measured data. The squared correlation coefficient (the zero lag of the normalized covariance function) between tone-burst data and simulations is found to be $R^2 = 0.90$, showing a nice covariance between simulations and data. The simulated click-evoked latencies are indicated by the symbols next to the 8-kHz tone-pulse results. The filled circles on the right show the corresponding measured click data taken from Elberling *et al.* (2010). The stimulus levels used for the simulations were the same as those for the tone-burst simulations, whereas the levels of the click in the experimental study of Elberling *et al.* (2010) are stated next to the respective data points. As for the high-frequency tone pulses, the model predicts a reduced dynamic range of wave-V latencies across levels compared to the measured values.

B. Simulation of broadband chirp-evoked wave-V amplitudes and latencies

The black lines in Fig. 6 shows the simulated wave-V amplitudes obtained for the five chirps described in Elberling *et al.* (2010), at the three levels tested. In addition, click-evoked wave-V amplitudes for the same stimulation levels are shown on the left. The “change of delay” abscissa refers to the delay differences between the 5700-Hz component to the 710-Hz component of the stimulus. This reflects that a chirp with a faster sweeping rate has a shorter duration. The click is represented by a 0-ms change of delay as all the frequency components have the same delay. The gray lines of Fig. 6 shows the corresponding

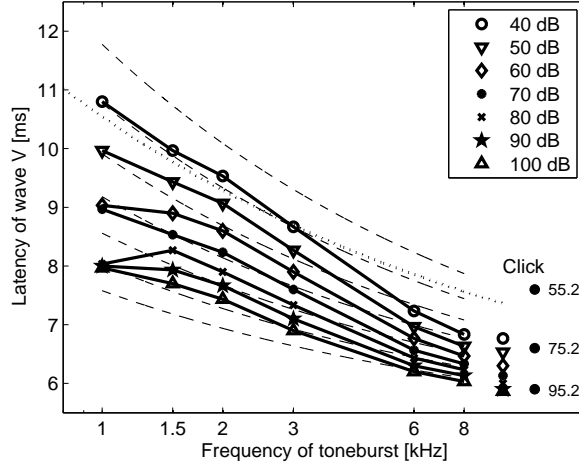


FIG. 5. Simulated (solid curves) and modeled (dashed curves based on eq. 9, dotted curve, based on Harte *et al.*, 2009) ABR wave-V latencies as a function of tone-burst center frequency and level. Each line fitted to Neely *et al.* (1988)’s empirical data corresponds to one simulated level. Open symbols to the right show simulated click-evoked ABR wave-V latencies, filled symbols show Elberling *et al.* (2010) measured click latencies. All levels are given in dB pe SPL.

measured data from Elberling *et al.* (2010). The squared correlation coefficient between data and simulations is $R^2 = 0.90$, demonstrating good covariance between simulations and data. The measured data shows that, for the highest stimulation level of 60 dB nHL, the chirp with a relatively short duration (chirp 2) i.e. a small delay difference between the low- and high-frequency stimulus components, had the largest wave-V amplitude. Chirp 2 thus represents the stimulus that is most effective at synchronizing the neural output across frequency. In contrast, for the stimulation levels of 40 dB nHL and 20 dB nHL, the corresponding maxima were found with chirp 3 and chirp 5, respectively, suggesting that other sweeping rates provided maximal synchronization across frequency. These key features observed in the measured data are also reflected in the simulations. The click-evoked responses show a smaller amplitude than those obtained with all chirps both in the data and the predictions. However, the maxima in the simulated functions are slightly shifted towards chirps with

shorter durations. Overall, the correspondence between simulations and measured data is remarkable and the results support the hypothesis that the dynamic nonlinear processes in the cochlea strongly affect ABR formation.

Figure 7 shows wave V latencies simulated (black lines) by the ABR model and measured (gray lines) by Elberling *et al.* (2010) in response to the click and the five chirps. The squared correlation coefficient between data and simulations is found to be $R^2 = 0.96$, indicating covariance of simulations and data. R^2 does not tell anything about the agreement between absolute latency values, it only shows that the data and simulation co-vary to a large degree. The measured latencies can probably be explained in terms of upwards spread of excitation (Elberling *et al.*, 2010) and the fact that the frequency region dominating the ABR response is 2 to 4 kHz (Eggermont and Don, 1980) for the lower levels of 20 and 40 dB HL (for higher levels the region broadens towards higher frequencies). As stimulus level is increased, the BM filters broaden and lower frequency parts of the stimulus will excite the main frequency region. The longer the chirp is, the earlier is the low frequency part of the stimulus presented and an early excitation of the main frequency region is possible. Thus, at high levels (e.g. 60 dB HL) and long chirp delays (e.g. chirp 5), the latency will be very short due to the early presentation of low frequencies and the upward spread of excitation. The simulated results show the same trends, i.e. that the shortest duration is observed for high stimulus levels and long chirp delays. However, the level-dependence seems, as in the previous simulation of tone bursts and clicks, much compressed.

V. DISCUSSION

This study evaluated the developed ABR model by comparing simulations with literature data, using clicks, tone-bursts and chirps as stimuli. The wave-V amplitudes simulated in response to a click presented at three stimulus-levels showed good correspondence to literature data, demonstrating that the overall calibration of the model was correct. Further, the correct level-dependence indicates that cochlear compression was well implemented.

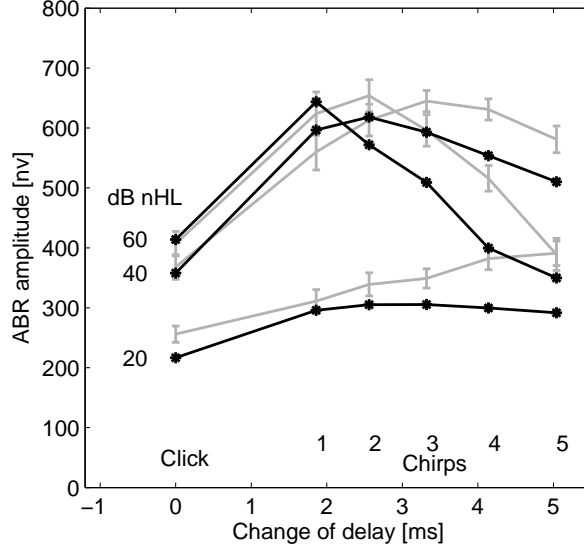


FIG. 6. Black lines: Simulated ABR wave-V amplitudes evoked by click and 5 chirps with different frequency-delay functions at three different stimulus levels. gray lines: ABR wave-V amplitudes evoked by the click and five chirps (Recorded by Elberling *et al.*, 2010). All simulations are well within one standard deviation of the measured value. Note that the error bars in the figure represents one standard error.

The latencies of the simulated tone-burst evoked ABRs showed good frequency-dependence, whereas the level-dependence was somewhat compressed. First, this shows that the travelling wave delay (the frequency-dependence) was modeled well. Second, the compressed level-dependence suggests that either the level-dependence of the BM tuning or the adaptation of the AN-IHC synapse was modeled imprecisely, or alternatively, that the assumptions underlying the UR were too extensive. This will be further discussed below. The chirp simulations showed a good correlation with literature data. The simulations of the five chirps with different sweeping rates at three different levels demonstrated that the current model was capable of simulating responses to complex stimuli and that the interaction between the travelling wave delay and the level-dependent BM tuning seems to be working well.

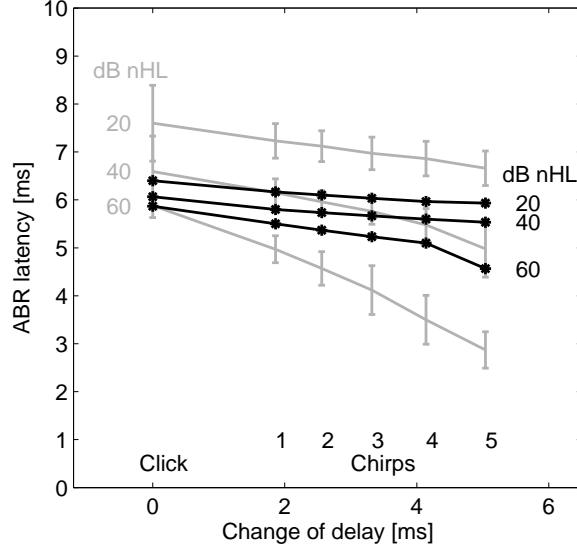


FIG. 7. Black lines: Simulated ABR wave-V latencies evoked by click and 5 chirps with different frequency-delay functions at three different stimulus levels. gray lines: ABR wave-V latencies evoked by the click and five chirps (Recorded by Elberling *et al.*, 2010). Note that the error bars represents one standard deviation.

A. Limitations of the conceptual approach

The assumption that all nonlinearity is restricted to the BM and AN and that the remaining processing is linear is an obvious over-simplification given the high complexity of neural processing within the brainstem. Specifically, the assumption that the rate functions in the MSO and AVCN within the brainstem are the same as in the AN is most likely erroneous (Dau, 2003). For example, it has been shown that neural synchronization in the AVCN can be enhanced compared with AN fibers, due to the convergence of inputs from two or more AN fibers on an AVCN cell and postsynaptic cells that require coincident input spikes before firing (Joris *et al.*, 1994). Furthermore, even though the human ABR may be largely generated by brainstem cells in the spherical cell pathway (Melcher and Kiang, 1996), there is probably also some contribution from other cell types such as globular and multipolar cells. There is still some controversy about the exact generating sites of the ABR

peaks beyond wave I. The whole modeling approach should therefore be considered as a rough approximation of the real neural mechanisms involved in the generation of brainstem potentials. Nevertheless, it appears that the chosen approach represents an effective approximation since major characteristics of the measured data can be accounted for. These major characteristics include the wave-V amplitude, the frequency dependence of the wave-V latency and, to a lesser degree, the level-dependence of the wave-V latency.

B. Effects of the unitary response function

In the present study, the UR was empirically obtained by deconvolving a grand average click ABR with the discharge rate function at the output of the AN model. The UR was only obtained once, for this 95.2 dB SPL click evoked grand averaged ABR, and all other stimulus conditions made use of this UR. Only using one UR derived from a single waveform ensured that the generality of the modeling framework could be tested. Simple linear convolution of a UR might be an over-simplification for several reasons. First, the UR can be assumed to be subject dependent. In the present study, all simulations were rerun using individually estimated UR functions from three different subjects (not shown explicitly). However, this only resulted in a change to the overall simulated response amplitudes, and introduced an individual latency offset. The differences were minimal and reflected inter-subject differences, keeping the same broad dynamics as observed for the grand averaged UR. Second, Chertoff (2004) investigated the level and frequency dependency of a UR used to model compound action potentials (CAP) in Mongolian gerbils. He showed that the UR has both a slight level and frequency dependence in this species (the first peak of the CAP-UR shifts up to 0.1 ms). However, no general formulation of the dependency was stated and no formulation of a level-dependent UR for humans has yet been attempted in the literature. Further, the interval between wave-I and wave-V peaks has been shown to be remarkably robust across stimulus level in ABR recordings (Don and Eggermont, 1978; Eggermont and Don, 1980), indicating that a level-dependent UR is not required. Contradictory to this, however,

Chertoff *et al.* (2010) measured compound action potential (CAP) latency in humans, and demonstrated that CAPs could have a smaller latency change with level than what has been reported for ABR wave-V latency (Serpanos *et al.*, 1997; Dau, 2003; Elberling *et al.*, 2010). This would tend to suggest that the wave-I (which is believed to have the same origin as the CAP) to wave-V interval, and thus the UR, should be level-dependent. It is unclear from the literature whether a level-dependent UR is in fact needed.

C. Wave-V latency dependency on frequency and level

Taking the variability on the measured data into account, the simulated tone-burst evoked response latencies showed reasonable agreement with the measured data (Harte *et al.*, 2009; Neely *et al.*, 1988) for the frequency range 1 - 8 kHz and for a level range of 40 - 100 dB SPL. In particular, for a given stimulation level, the change of latency with frequency can be accounted for quite well by the model. However, the latency change with level was smaller in the simulations than in the data, particularly at high frequencies. Click-evoked ABRs were also simulated to test the model’s performance when considering broadband excitation. The simulated click-evoked latencies of the present study decreased by only 0.6 ms for a 40 dB increase of stimulus level (from 55 to 95dB pe SPL), corresponding to -0.015 ms / dB, which is in contrast to the decrease of a little less than 2 ms observed in the Elberling *et al.* (2010) data, corresponding to -0.043 ms / dB. Other literature studies report latency decreases in the order of -0.043 ms / dB (Serpanos *et al.*, 1997) and -0.046 ms / dB (Dau, 2003) for similar stimulus ranges. Even though the variability on the individual data set was high (a standard deviation of 0.81 ms on average for Elberling *et al.*, 2010), the discrepancy between model and data is noticeable.

BM filter tuning and IHC-AN synapse adaptation determine the level dependency of ABR wave-V latency in the model. The ABR model latency change of -0.015 ms / dB is a small improvement over the earlier modeling study by Dau (2003) who obtained latency changes of -0.005 ms / dB for a similar stimulus level range. Additional simulations, where

the BM tuning was altered (and reported in Rønne *et al.*, 2011), demonstrated that the improvement was the result of the use of the humanized version of Zilany and Bruce (2007)’s AN model instead of the model by Heinz *et al.* (2001). The humanized AN model uses the sharper tuning estimates from Shera *et al.* (2002) (see Ibrahim and Bruce, 2010) while Heinz *et al.* (2001) used the estimates of Glasberg and Moore (1990). The filters of Shera *et al.* (2002) (derived at only 40 dB SPL) are more sharply tuned than those described in Glasberg and Moore (1990) since they were estimated based on behavioral forward-masking data and otoacoustic emission data. In contrast, the estimates of Glasberg and Moore (1990) are based on behavioral simultaneous masking, which is affected by peripheral suppression (Shera *et al.*, 2002; Bentsen *et al.*, 2011). However, there is still a substantial discrepancy between the simulated and the measured latency-level range. As shown in Fig. 3, the model incorporates a level dependence in the C1 filter tuning factor. While the empirical evidence for the frequency dependence of the tuning factor (Shera *et al.*, 2002, 2010; Bentsen *et al.*, 2011) is well documented, there is little data existing for the level dependence in humans. This quality factor level dependence will strongly affect wave-V latency and could be one reason for the underestimation observed in the simulations. Additionally, neural adaptation in the IHC-AN synapse enhances the onset and leads to shorter delays. For analysis purposes (data not shown in this paper, see Rønne *et al.*, 2011), click-evoked wave-V latencies were simulated using an altered version of the ABR model where the IHC output of the AN model was used, thus not including any adaptation process. However, while adaptation affected the absolute value of the wave-V latency in the framework of the present model, it did not have a major impact on the latency variation with level. A possible level-dependence of the UR, though not implemented in the model, could also affect the ABR wave-V latency. As discussed above, the literature is inconclusive on this matter. Further, Chertoff *et al.* (2010)’s CAP latencies decrease by -0.030 ms / dB over the level range of 75 to 105 dB SPL. So, even if a level-dependent UR was implemented to account for the difference in latency change between Chertoff *et al.* (2010) and Elberling *et al.* (2010), the AN model would still under predict the wave-V latency. It thus remains unclear why the model fails to account

more accurately for the level-dependent behavior of wave-V latency.

D. Across-frequency synchronization for broadband stimulation

When considering effects of level-dependent neural synchronization across frequency, the simulations illustrate the crucial role of nonlinear cochlear processing for the formation of brainstem responses to transient stimuli. The chirps presented in Elberling *et al.* (2010) were considered here as “critical” stimuli to challenge and evaluate the model. The results support the hypothesis that the dynamic behavior of ABR generation is mainly due to peripheral mechanisms as all processing at higher neural stages beyond the level of the AN was essentially considered as a linear filter. Further, the results reinforce the need to have level dependent chirp stimuli to get maximum wave-V amplitude clinically (Elberling and Don, 2010).

E. Perspectives

The model might be useful as a tool for studying consequences of different types of cochlear hearing impairment on the evoked potential waveform, provided that pathology can be adequately simulated in the model. Furthermore, brainstem responses to complex stimuli (cABR), such as consonant-vowel utterances, have been considered as an objective index of the neural transcription of features (e.g. temporal, spectral) that are important for speech understanding in quiet and noise (e.g. Anderson *et al.*, 2011). The model could be used to analyze which spectro-temporal characteristics of the speech-evoked patterns can be accounted for by cochlear processes. Finally, an important step would be to consider “steady-state” responses (SSR) obtained with temporally fluctuating stimuli such as complex tones or amplitude modulated tones or noises. These responses are assumed to be generated by units in the auditory brainstem and in the primary auditory cortex (e.g. Kuwada *et al.*, 1986). Therefore, the corresponding unitary response would have to be extended by a middle-latency component. It is not clear, to what extent such a convolution approach can be

successfully applied to middle-latency responses (MLR), to transients as well as amplitude modulation following responses. Regarding MLRs, at least, it has been shown that the “classical” SSR to click trains presented at a 40 clicks/sec repetition rate can be modeled reasonably well using a linear convolution approach (Bohorquez and Özdamar, 2008; Junius and Dau, 2005).

VI. SUMMARY AND CONCLUSION

A computational model for the generation of ABRs to transient stimuli was presented. The model was based on the assumption that an ABR can be simulated as the convolution between an instantaneous discharge rate function and a unitary response. The instantaneous discharge rate function was obtained from a state-of-the-art nonlinear AN model (Zilany and Bruce, 2006). The UR was derived “empirically” as the deconvolution between the simulated instantaneous discharge rate AN function in response to a click stimulus and measured average click-evoked ABR.

The model was evaluated by comparing the predicted responses to measured ABR data from the literature. It was shown that a realistic simulation of the level-dependent signal processing in the cochlea is essential for the interpretation of ABR to tone pulses, clicks and chirps presented at various stimulation levels. In particular, the model could account reasonably well for the nonlinear wave-V amplitude behavior as a function of chirp stimulus level and sweeping rate which supports the strong role of cochlear nonlinearities, such as compression and level-dependent tuning, for the formation of ABR. However, the model clearly underestimated the level dependence of the response (wave-V) latency and it remained unresolved in the framework of the modeling work presented here what mechanisms are responsible for the relatively large latency changes with level observed in the data.

Overall, the developed model can provide insight into the complex nature of ABR generation. It can be used to investigate the representation of other types of stimuli (such as speech in noise) or to study effects of (different types of cochlear) hearing impairment on the

predicted potential patterns. Furthermore, the modeling approach might provide a basis for the investigation of longer-latency responses, such as steady-state responses to amplitude modulated tones and noises.

The ABR model including, grand average ABR, UR, and key simulations, is included in the Auditory Modeling (AM) toolbox (Søndergaard *et al.*, 2011) and can be downloaded from: <http://amtoolbox.sourceforge.net/> (date last viewed 02/14/12).

Endnotes

1. The ISO 389-6:2007 standard specifies that the peak-to-peak reference equivalent threshold sound pressure level (peRETSPL) is 43.5 dB peRETSPL, for an ER2 earphone connected to an IEC 60711 coupler through the external ear simulator DB 0370. Unfortunately, the tube diameter for the standard ear tip for the ER2 earphone (ER1-14) is 1.37mm whereas it is 3mm for the DB 0370. This mismatch creates an acoustic horn effect which affects the spectrum (Richter and Fedtke, 2005; Elberling *et al.*, 2012) and thus the level. Richter and Fedtke (2005) also measured the peak-to-peak reference equivalent threshold sound pressure level (peRETSPL) for an ER2 earphone connected to a head and torso simulator (HATS) and found it to be 35.2 dB. The change of the external ear simulator from the DB 0370 (ISO 389-6:2007) to the HATS (Table 7 Richter and Fedtke, 2005), results thus in a 8.3 dB change in the peRETSPL. As the acoustic horn effect is not present in human fittings, the ISO 389-6:2007 does not represent the pe SPL at the eardrum. For the modeling presented in the present study, the HATS measurements from Richter and Fedtke (2005) were therefore used as the reference.

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Frequency kHz	Total Length	
	ms	cycles
0.5	10	5
0.75	7	5.25
1	5	5
1.5	5	7.5
2	5	10
3	3.4	10.2
4	2.5	10
6	1.7	10.2
8	1.25	10

TABLE I. Tone burst stimuli used, with durations represented in ms and as number of cycles.

k	d	Chirp
0.4501	0.6373	5
0.2207	0.5468	4
0.1083	0.4563	3
0.0531	0.3658	2
0.0260	0.2753	1

TABLE II. Values of the paired parameter, k and d , which define the delay-frequency function (eq. 8)

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- FIG. 3 Filter bandwidths, Q_{ERB} , derived from the output of the C1 filter path (from Fig. 2). The dashed curve shows Q_{ERB} estimates based on Shera *et al.* (2002)'s data obtained at a stimulation level of 40 dB pe SPL. 12
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FIG. 5	Simulated (solid curves) and modeled (dashed curves based on eq. 9, dotted curve, based on Harte <i>et al.</i> , 2009) ABR wave-V latencies as a function of tone-burst center frequency and level. Each line fitted to Neely <i>et al.</i> (1988)'s empirical data corresponds to one simulated level. Open symbols to the right show simulated click-evoked ABR wave-V latencies, filled symbols show Elberling <i>et al.</i> (2010) measured click latencies. All levels are given in dB pe SPL.	17
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